Exhibit E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Xiaofang WANG

Application No.: 14/413,290

Confirmation No.: 6606

Filed: January 7, 2015

Art Unit: 1632

For: MESENCHYMAL-LIKE STEM CELLS DERIVED FROM HUMAN EMBRYONIC STEM CELLS, METHODS AND USES THEREOF

Examiner: Ton, Thaian N

AMENDMENT UNDER 37 C.F.R. §1.111

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Dear Sir:

In response to the non-final Office Action mailed July 28, 2016, please amend the above-identified U.S patent application under 37 C.F.R. §1.111 as follows and consider the Petition for a 3-month extension of time from October 28, 2016 to and including January 28, 2017, and the required fee. The Commissioner is hereby authorized to charge any unpaid fees deemed required in connection with this submission to Deposit Account No. 50-4570.

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

Amendments to the Claims:

Pursuant to 37 C.F.R. § 1.121 the listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A method for producing human embryonic stem cell-derived mesenchymal stem cells (hES-MSCs), comprising:

a. culturing human embryonic stem cells [[with]] in a serum free medium [[media]] with at least one ~~or without~~ GSK3 inhibitor at a concentration ranging from 0.05 μM to 0.2 μM, wherein the human embryonic stem cells are cultured in the absence of feeder cells ~~inhibitors~~;

b. culturing human embryonic stem cells in a serum-free medium [[media]] comprising vascular endothelial growth factor (VEGF) and bone morphogenic protein 4 (BMP4) in an amount sufficient to induce formation of ~~differentiation into~~ embryoid bodies;

c. adding at least one growth factor to the culture, wherein the growth factor is in an amount sufficient to expand human hemangio-colony forming cells;

d. disaggregating the hemangio-colony forming cells into single cells; and

e. culturing the single cells in a medium [[media]] containing serum, knockout serum replacement (KOSR), or in a [[other]] serum-free medium ~~in an amount sufficient~~ to induce differentiation of the single cells into mesenchymal stem cells;

wherein at least about 90% of the hES-MSCs ~~mesenchymal stem cells~~ express CD73, said hES-MSCs [[MSC]] having the following characteristics: (i) contain >95% of cells expressing group-1 markers; (ii) contain >80% of cells expressing group 2 markers; (iii) contain <5% of cells expressing group-3 markers (iv) expressing IL-10 and TGFβ; (v) contain <2% of cells expressing IL-6, IL-12 and TNFα; and (vi) contains <0.001% of cells co-expressing all group-4 markers, wherein group-1 markers are CD73, CD90, CD105, CD146, CD166, and CD44, group-2 markers are CD13, CD29, CD54, CD49E, group-3 markers are CD45, CD34, CD31 and SSEA4, and group-4 markers are OCT4, NANOG, TRA-1-60 and SSEA4.

2. (Currently Amended) The method of claim 1, wherein the hES-MSCs ~~cells~~ do not express IL-6, IL12 and TNFα.

3. (Currently Amended) The method of claim 1, wherein the hES-MSCs ~~cells~~ express TGF-beta1, TGF-beta2 and IL10.

4. (Currently Amended) The method of claim 1, wherein the hES-MSCs ~~cells~~ do not express CCL2, MMP2 and RAGE.

5. (Currently Amended) The method of claim 1, where in the hES-MSCs ~~cells~~ have low expression of IFNγR1, IFNγR2 as compared to bone marrow derived mesenchymal stem cells ~~BM-MSC~~.

6. (Withdrawn) A method of modifying mesenchymal stem cells to produce a population of modified MSC having the following characteristics: (i) contain >95% of cells expressing group-1 markers; (ii) contain >80% of cells expressing group 2 markers; (iii) contain <5% of cells expressing group-3 markers (iv) expressing IL-10 and TGFβ; (v) contain <2% of cells expressing IL-6 , IL-12 and TNFα; and (vi) contains <0.001% of cells co-expressing all group-4 markers, wherein group-1 markers are CD73, CD90, CD105, CD146, CD166, and CD44, group-2 markers are CD13, CD29, CD54, CD49E, , group-3 markers are CD45, CD34, CD31 and SSEA4, and group-4 markers are OCT4, NANOG, TRA-1-60 and SSEA4.

7 - 12. (Canceled)

13. (Previously Presented) The method of claim 1, further comprising a step of irradiating the mesenchymal stem cells.

14. – 18. (Cancelled)

19. (Withdrawn) A cell culture comprising the hES-MSC prepared by the method of claim 1.

20. – 22. (Canceled)

23. (Withdrawn) A pharmaceutical preparation comprising the hES-MSC prepared by the method of claim 1 and a pharmaceutical acceptable carrier.

24. – 26. (Canceled)

27. (Withdrawn) A method for preventing or treating a T cell and/or B cell related autoimmune disease comprising administering to a subject in need thereof the hES-MSC prepared by the method of claim 1, an amount sufficient to ameliorate or alleviate at least one symptom of the T cell related autoimmune disease or reverse the T cell and /or B cell related autoimmune disease.

28. – 42. (Canceled)

43. (Withdrawn) A method for preventing or treating a multiple sclerosis comprising administering to a subject in need thereof the hES-MSC prepared by the method of claim 1, an amount sufficient to ameliorate or alleviate at least one symptom of the disease or reverse the disease.

44. – 58. (Canceled)

59. (Withdrawn) A method of delivering an agent through the blood-brain barrier and/or the blood-spinal cord barrier, said method comprising the steps of: attaching the agent to a MSC to form a MSC-agent complex; and administering the MSC-agent complex to a subject in need thereof, wherein the human embryonic-mesenchymal stem cell is capable of crossing the blood-brain barrier and/or the blood-spinal cord barrier and the agent is for the treatment, prevention or diagnosis of a disease or injury in the subject in need thereof.

60. (Withdrawn) A kit comprising the hES-MSC prepared by the method of claim 1 and a carrier.

61. (Withdrawn) The kit of claim 60 further comprising a thawing reagent, immunosuppressive enhancer, anti-histamine.

62. (Currently Amended) The method of claim 13 wherein the mesenchymal stem cells are irradiated with gamma-irradiation ~~gama-irradiation~~.

63. – 66. (Canceled)

67. (Currently Amended) The method of claim 1, wherein the hES-MSCs are modified by genetic modification, epigenetic regulation, small molecule, nutraceutical, natural compound, or antibody treatment.

68. – 82. (Canceled)

83. (Currently Amended) The method of claim 1, further comprising co-culturing the hES-MSCs with ~~bone marrow~~ hematopoietic stem cells ~~and/or umbilical-cord hematopoietic stem cell~~.

84. – 87. (Cancelled)

88. (Currently Amended) The method of claim 83, wherein the ~~hES-MSC is co-cultured with~~ hematopoietic stem cells comprise bone marrow hematopoietic stem cells and/or umbilical-cord hematopoietic stem cells.

89. – 92. (Cancelled)

93. (New) The method of claim 1, wherein the GSK3 inhibitor is (2'Z,3'E)-6-Bromoindirubin-3'-oxime (BIO).

REMARKS

Claims 1 – 6, 13, 19, 23, 27, 43, 59 – 62, 67, 83, 88 and 93 are pending in this case. Claims 1 – 5, 62, 67, 83 and 88 have been amended. Claims 6, 19, 23, 27, 43 and 59 – 61 have been withdrawn. Claims 7 – 12, 14 – 18, 20 – 22, 24 – 26, 28 – 42, 44 – 58, 63 – 66, 68 – 82, 84 – 87 and 89 – 92 have been cancelled without prejudice. Claim 93 is new.

Support for "from 0.05 μM to 0.2 μM" of a GSK3 inhibitor can be found at least at page 18, lines 17-19, as well as page 70, lines 27-28, of the specification as filed. Support for "the human embryonic stem cells are cultured in the absence of feeder cells" can be found at least at page 18, lines 16-17; and page 72, lines 4-5, of the specification as filed. Support for new claim 93 can be found at least at page 13, lines 31-32, as well as page 70, lines 27-28, of the specification as filed. Support for the other claim amendments can be found at least in the original claims. No new matter has been introduced with this amendment. Entry of the amendments is respectfully requested. Amendment and cancellation of the claims herein are not to be construed as acquiescence to any of the rejections/objections made in the instant Office Action or in any previous Office Action, and were done solely to expedite prosecution of the application. The Applicants hereby reserve the right to pursue the claims as originally filed, or substantially similar claims in one or more subsequent patent applications. The Applicants also reserve the right to rejoinder. Once the elected claims are found allowable, all withdrawn claims that include all the limitations of an allowable claim should be rejoined.

I. Claim Objections

Claims 62, 67, 83 and 88 are objected to because of certain informalities. Claims 62, 67, 83 and 88 have been amended to correct the informalities. As such, the claim objections have been overcome.

II. Rejections Under 35 USC §112, Second Paragraph

Claims 1-5, 13, 62, 67, 83 and 88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The claims have been amended to address the Examiner's rejections. As such, the rejections have been overcome.

III. Rejections Under 35 USC §112, Fourth Paragraph

Claim 88 is rejected under 35 U.S.C. 112, 4th paragraph, as being of improper dependent form. Claims 83 and 88 have been amended to address the Examiner's rejections. As such, the rejections have been overcome.

IV. Rejections Under 35 U.S.C. 102

Claims 1-5, 13 and 67 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by WO 2013/082543 (Lanza et al., published June 6, 2013, hereinafter "Lanza").

Lanza was filed on November 30, 2012, and claims priority to U.S. Provisional Application No. 61/565,358 which was filed on November 30, 2011. Lanza was published on June 6, 2013. Without conceding to the rejection and solely to advance prosecution, the Applicants submit a declaration under 37 C.F.R. §1.131 (Exhibit A), swearing behind the priority date and publication date of Lanza. Therefore, Lanza does not constitute prior art, and the 102(a) and 102(e) rejections are rendered moot.

Furthermore, it is the Applicants' position that the pending claims, as amended, does not claim the same patentable invention and are not anticipated by Lanza. To anticipate a claim, the reference must teach each and every element of the claim. MPEP § 2131 ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference", quoting Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, Fed. Cir. 1987).

In fact, Lanza does not disclose each and every element of the amended claims. Specifically, Lanza fails to teach culturing human embryonic stem cells in a medium with "at least one GSK3 inhibitor at a concentration ranging from 0.05 μM to 0.2 μM" as recited in amended claim 1. Nor does Lanza teach that "the human embryonic stem cells are cultured in the absence of feeder cells" as recited in amended claim 1.

Rather, Lanza discloses that the human embryonic stem cells are cultured in the presence of feeder cells: "The ESCs may be initially co-cultivated with murine embryonic feeder cells (MEF)

cells." Lanza, paragraph [078]. Lanza also teaches at paragraph [0334] that "[h]uman ES cells were generally cultured on irradiated or mitomycin-C treated mouse embryonic fibroblasts (MEF) feeder cells in Human ES Cell Growth Medium".

Therefore, Lanza does not anticipate claim 1. As amended, claims 2-5, 13 and 67 are dependent on claim 1 and, therefore, incorporate each element of claim 1. See MPEP § 608.01(n) ("a dependent claim is directed to a combination including everything recited in the base claim and what is recited in the dependent claim. It is this combination that must be compared with the prior art, exactly as if it were presented as one independent claim"). Accordingly, because it does not teach each and every element of claim 1, Lanza does not teach each and every element of claims 2-5, 13 and 67.

Therefore, the Applicant respectfully submits that the rejections under 35 U.S.C. § 102(a) and (e) are rendered moot.

V. Rejections Under 35 USC § 103

Claims 1-5, 13, 62 and 67 are rejected under 35 U.S.C. 103(a) as being obvious over Lanza when taken with CA 2792802 (Kato et al., hereinafter "Kato").

Claims 1-5, 13, 67, 83 and 88 are rejected under 35 U.S.C. 103(a) as being obvious over Lanza when taken with Briquet et al., Haematologica, 95(1): 47-56, 2010 (hereinafter "Briquet").

As discussed above, in view of the declaration under 37 C.F.R. §1.131 (Exhibit A), swearing behind the priority date and publication date of Lanza, Lanza does not constitute prior art. As Kato was published on September 15, 2011, it is not a proper prior art reference either in view of the declaration under 37 C.F.R. §1.131 (Exhibit A). As such, Rejections of the claims under 35 U.S.C. 103(a) should be withdrawn.

CONCLUSION

In view of the foregoing, each of the presently pending claims in this application is believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to allow this application to issue.

The Examiner is respectfully requested to contact the undersigned at the telephone number indicated below if the Examiner believes any issue can be resolved through either a Supplemental Response or an Examiner's Amendment.

Applicant submits that no additional payment is required for this filing. However, in the event that any other fees are required, the Commissioner is authorized to charge any deficiency or credit any excess in this fee to Deposit Account No. 50-4570.

Dated: January 17, 2017

Respectfully submitted,

By 

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Exhibit A:

DECLARATION UNDER 37 C.F.R. § 1.131

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Xiaofang WANG

Application No.: 14/413,290

Confirmation No.: 6606

Filed: January 7, 2015

Art Unit: 1632

For: MESENCHYMAL-LIKE STEM CELLS DERIVED FROM HUMAN EMBRYONIC STEM CELLS, METHODS AND USES THEREOF

Examiner: Ton, Thaian N

DECLARATION UNDER 37 C.F.R. § 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

We, Xiaofang Wang and Ren-He Xu, hereby declare the following, based on our own knowledge, information and belief:

1. We are the original and joint inventors of the subject matter as set forth in the claims, as originally filed in U.S. Application Serial No. 14/413,290 ("the '290 application"), filed on January 7, 2015. We are also the original and joint inventors of the subject matter as set forth in the claims, as amended in the Amendment, filed herewith (hereinafter the "Invention").

2. We had possession of the Invention in the United States of America before November 30, 2011, the priority date of WO 2013/082543 to Lanza et al. We also had possession of the Invention in the United States of America before June 6, 2013, the publication date of WO 2013/082543 to Lanza et al. 37 C.F.R. 1.131. Records evidencing such possession are attached as Exhibits B - D.

3. Exhibit B includes selected slides from a department presentation (date redacted), before the priority date and publication date of Lanza. Exhibit B shows reduction to practice of methods for producing mesenchymal stem cells by culturing human embryonic stem cells in the presence of a GSK3 inhibitor; culturing human embryonic stem cells to induce formation of embryoid bodies; expanding human hemangio-colony forming cells (hemangioblasts); and producing mesenchymal stem cells (MSCs).

Exhibit C includes flow cytometry data (date redacted), before the priority date and publication date of Lanza. Exhibit C shows MSCs positive for both CD73 and CD90 markers (see the upper-right quadrant of the right panel of Exhibit C). The MSCs were generated by an embodiment of the claimed method.

Exhibit D includes lab notes (date redacted), before the priority date and publication date of Lanza. Exhibit D shows reduction to practice of methods for producing mesenchymal stem cells by culturing human embryonic stem cells in the presence of a GSK3 inhibitor; culturing human embryonic stem cells to induce formation of embryoid bodies; expanding human hemangio-colony forming cells (hemangioblasts); and producing mesenchymal stem cells (MSCs).

All of this work was performed in the United States of America.

4. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 12th day of January, 2017.

Xiaofang Wang

Signed this 12th day of January, 2017.

Ren-He Xu

Exhibit B

Selected slides from a department presentation dated before the priority date and publication date of Lanza

High efficiency Differentiation of HSC and MSC from human embryonic stem cells Feeder free and Serum free system

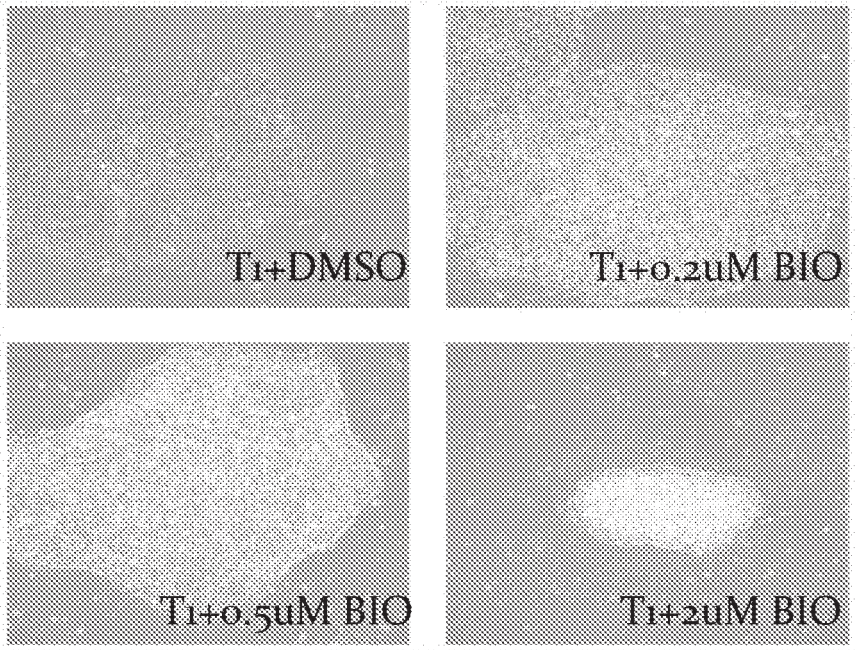
Xiaofang Wang

Using small molecular(BIO) to improve mTeSR1 culture

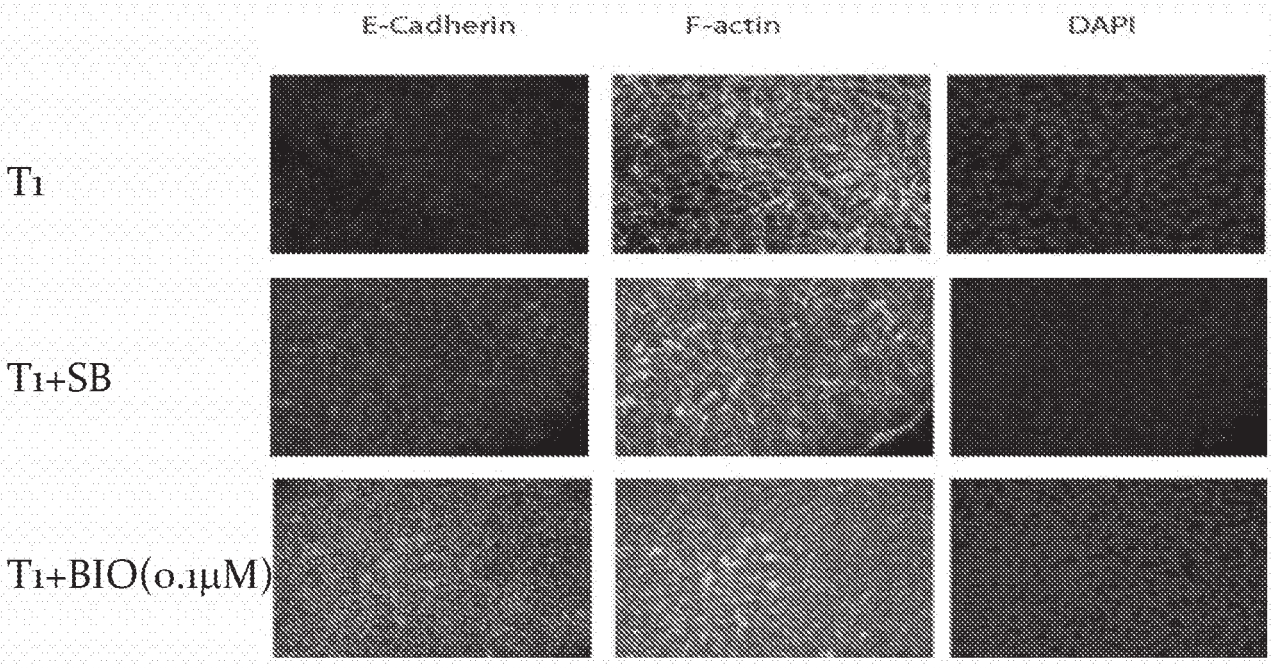
- E-cadherin has been shown to support mESC attachment
- SB (TGFb inhibitor) increases "ES cell" expansion and EB formation yield due to increased E-cadherin expression (unpublished)
- SB cannot be used to maintain ES cell culture
- We found another small molecular(BIO) can maintain hES culture for up to 12 passages without change pluripotency ,
- BIO significantly increase E-cadherin expression
- BIO, a GSK_3 inhibitor

0.1-0.2uM BIO is ideal for hES culture

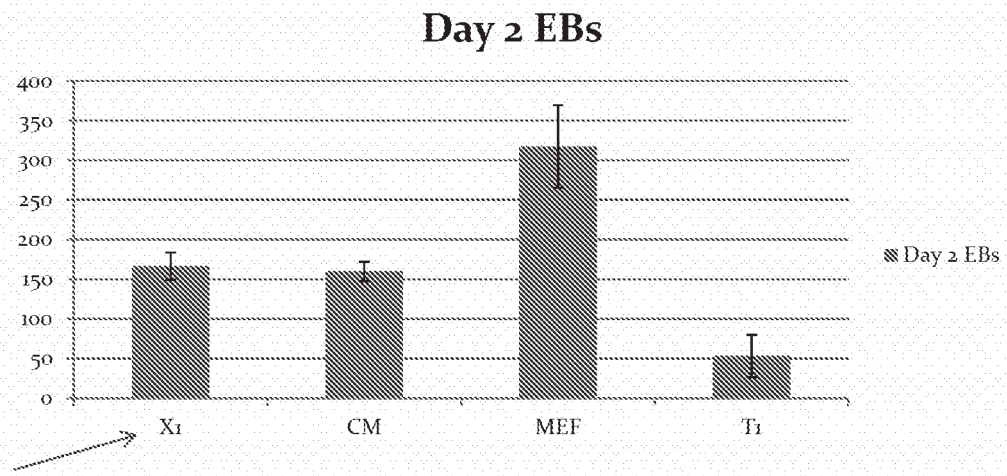
high concentration result in cell death and differentiation



Low concentration BIO also enhances E-Cadherin expression in hESCs in mTeSR1



BIO increases EB formation



From hESC in mTESR1(T1)+BIO

Hemangioblast formation from hESC cultured in T1 plus ROCKi and/or BIO

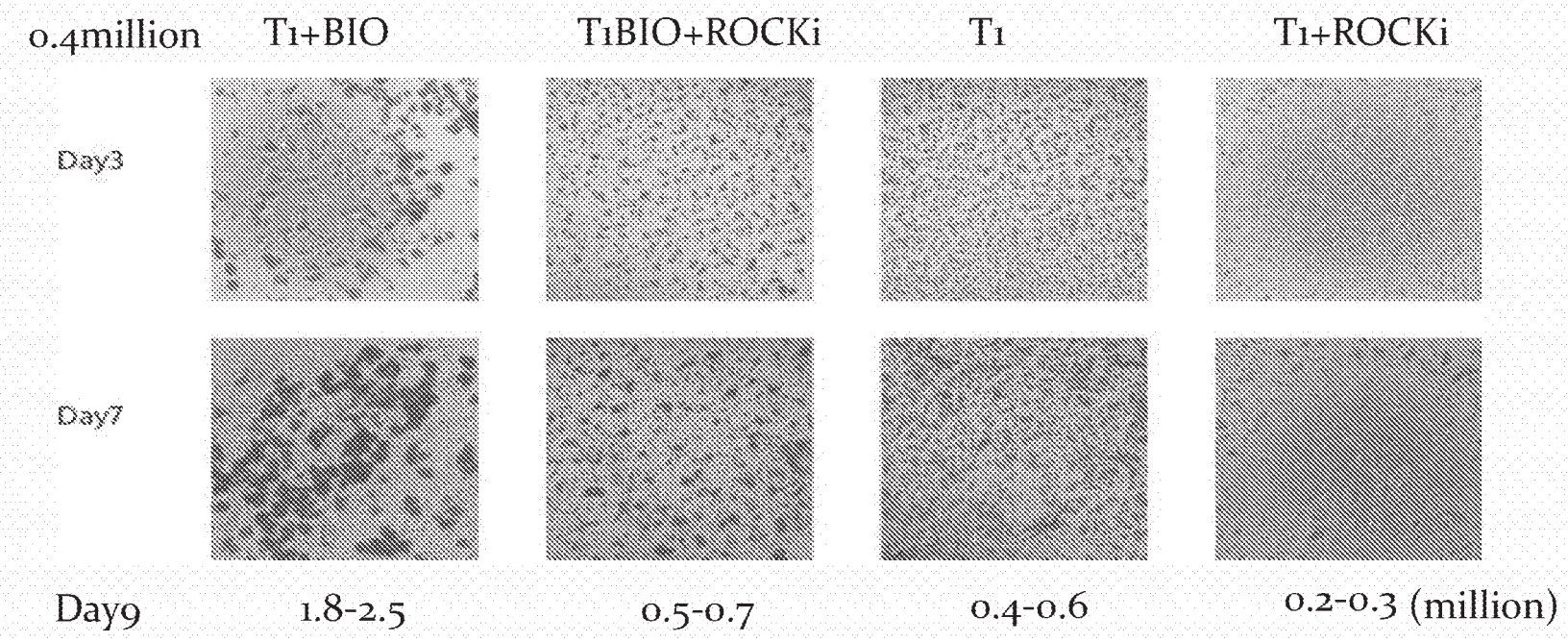
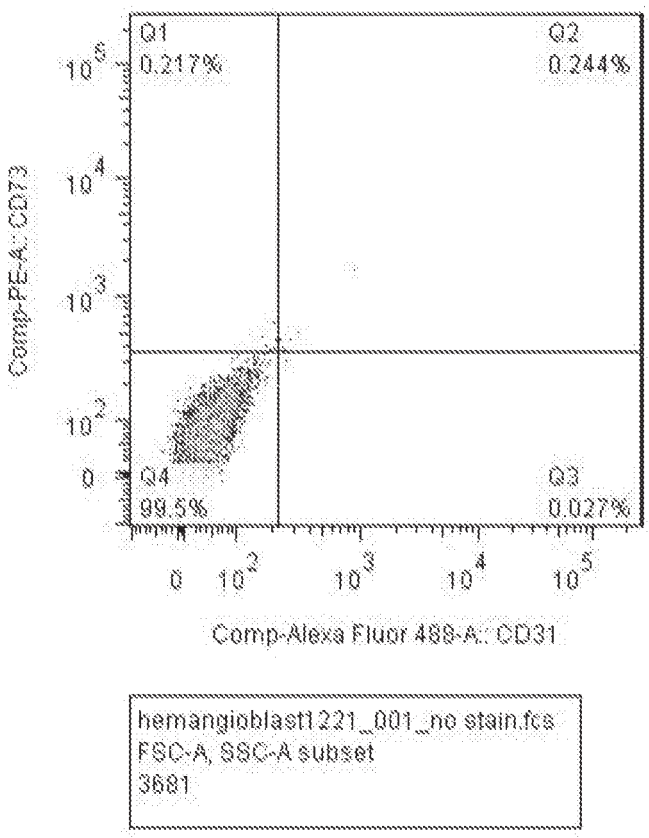


Exhibit C

Flow cytometry data dated before the priority date and publication date of Lanza


Q1
0.217%
Q2
0.244%
Q4
99.5%
Q3
0.027%
Comp-PE-A:: CD73
Comp-Alexa Fluor 488-A:: CD31
hemangioblast1221_001_no stain.fcs
FSC-A, SSC-A subset
3681

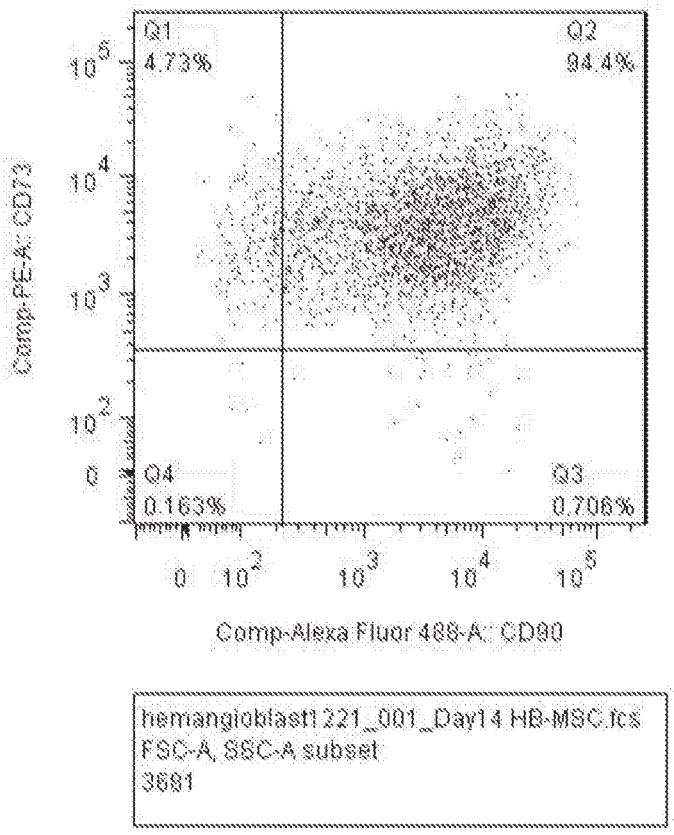

Q1
4.73%
Q2
94.4%
Q4
0.163%
Q3
0.706%
Comp-PE-A:: CD73
Comp-Alexa Fluor 488-A:: CD90
hemangioblast1221_001_Day14 HB-MSC.fcs
FSC-A, SSC-A subset
3681

Exhibit D

Lab notes dated before the priority date and publication date of Lanza

Project No. _____

Book No. _____

Page No. ____

D. MSC deck. Day 14. check. autoclave Tips

CD105, CD73. CD45, CD34.

2. run WB. check. B20, Ecad Ncad.

3. purify DNA. ligation.

4 Grant.

5 paper.

CD73 Color CD45. stain. x3.

4. 1.4.

WB

Snail ~1

N-cad

E-cad

β-actin

5. GSK3β phospho.

To Page No. ____

ded by: | Date | Verified by: | Date

Project No.

Book No. TITLE

From Page No.

Day 9

Staining.

Day 14

1) No staining

2) CD90 CD73 CO45.

3) CD31. CD13. CD105.

4) CD29 CD44.

5) CD54. CD44.

Make Bio treated AB

1ml buff use. 1) 0.2ug/ml Bio + 0.2...

2) 0.2ug Bio + Rocki.

(TI) 1) O... Rocki.

α647 Sal Ab. SSEA4 73 105

To Page

Recorded by: Date Verified by: Date